Rejection of Claims 1, 4 and 31 Under 35 U.S.C. §112, Second Paragraph

In paragraph 17 of Paper No. 8, claims 1, 4 and 31 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that "[i]t is unclear what the metes and bounds of the term 'nonimmunogenic' are."

Applicants respectfully traverse this rejection as it applies to the new claims containing this language. As newly submitted, the claims are drawn to therapeutic compositions including at least one peptide comprising at least one T cell epitope of a protein antigen and having a reproducible, defined sequence of amino acid residues and to methods of using the compositions to down regulate an antigen specific immune response in humans subject to said antigen specific immune response. Each of the newly presented independent claims (with the exception of claim 101 which is directed towards mimic peptides) requires a T cell epitope containing peptide in the composition. In one embodiment, the claimed compositions are administered in "non-immunogenic form". The phrase "in non-immunogenic form" is art-recognized and an example of a "non-immunogenic" form described in the present specification is a form "not containing adjuvant" (see e.g., page 6, line 27, and page 7, line 15 of the specification). Therefore, Applicants respectfully submit the metes and bounds of the term "non-immunogenic", as used in newly presented claims are clearly set forth in Applicants' disclosure. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Objection to the Specification and Rejection of Claims 1-43 Under 35 U.S.C. §112, First Paragraph

In paragraphs 18-20 of Paper 8, the specification is objected to and claims 1-43 are rejected under 35 U.S.C. §112, first paragraph, as failing to adequately describe or

enable the claimed invention. Each of the grounds for rejection set forth in paragraphs 18-20 is respectfully traversed for the following reasons.

The Examiner first states in paragraph 18(A) that the claim limitation to use of "nonimmunogenic" peptides is not adequately supported since the claimed compositions induce immune responses in human patients, as described, for example, at page 23, line 26 of the specification. However, Applicants respectfully point out that none of the newly presented claims recite "nonimmunogenic peptides", as suggested by the Examiner.

The new claims are directed to therapeutic compositions capable of down regulating an antigen specific immune response in humans, and to methods of using these compositions to treat humans sensitive to an antigen. The compositions contain one or more peptides having a reproducible, defined sequence of amino acid residues. The peptide comprises at least one T cell epitope of a protein antigen. In one embodiment, the claimed compositions are administered "in non-immunogenic form". No where do the claims recite "nonimmunogenic peptides".

As described in detail in the specification, the claimed compositions are administered to humans such that down regulation of an antigen specific immune response to an antigen of interest is achieved. Down regulation of an antigen specific immune response occurs when disease symptoms in a human sensitive to a protein antigen are reduced or eliminated, and/or the onset or progression of disease symptoms is prevented or slowed. One mode of achieving down regulation of an antigen specific immune response in a human is to administer the claimed composition in "non-immunogenic form". The peptide included in the composition contains at least one T cell epitope and, thus, is capable of inducing an immune response. While not being limited to any theory, it has been shown that peptides that contain at least one T cell epitope and, thus, are capable of eliciting a T cell response such as stimulation (i.e., proliferation or

lymphokine secretion) when administered in immunogenic form (to an individual primed with the offending protein or a peptide thereof) are than capable of inducing T cell non-responsiveness or down regulation when administered in non-immunogenic form (Jenkins, M.K., and Schwartz, R. H. *J. Exp. Med.* 165:302-319 (1987)).

In paragraph 18(B), the Examiner asserts that "[t]he test data from the human phase II study disclosed on page 24, line 2 of the specification, cannot be adequately evaluated because the results are presented as a summary, e.g., the total allergy score of 80% of the patients improved." In particular, the Examiner questions how the total allergy score was calculated and whether the study results were statistically significant *vis-a-vis* control group total allergy scores.

At page 21 of the specification, Applicants describe phase II clinical studies of the safety and activity of peptides X and Y from the cat allergen, *Fel d* I. These studies evaluated the sensitivity of 92 cat-allergic patients to natural cat exposure at time points prior to and following treatment with 7.5 μg, 75 μg, or 750 μg of peptide. Patients' sensitivity to cat exposure was assessed by measurement of symptom scores and pulmonary function during a 60 minute period in a small room containing two cats. In particular, patients were rated on a five point scale with respect to nose, eye and lung symptoms. Patients were also evaluated on the basis of "total allergy," or a combination of all parameters assessed for each subject.

It is the Examiner's position that the data presented for the above summarized phase II study "cannot be adequately evaluated because the results are presented as a summary, e.g., the total allergy score." However, Applicants respectfully submit that the data obtained from the phase II studies using peptides X and Y, and presented in graphical form in Figure 1, is an accurate indication of the efficacy of the instantly claimed compositions and can be adequately evaluated by one of ordinary skill in the art. The techniques used in this study are well accepted in the art. Furthermore, the data is

presented for individual subgroups of symptoms (e.g., nose and lung), as well as for total allergy (i.e., combination of all symptoms evaluated). Therefore, contrary to the Examiner's assertion, the data for the phase II cat studies is not presented as a "summary" which is incapable of evaluation. Rather, the data provides a quantified assessment of the improvement in allergic symptoms for patients on a per subgroup of symptom basis, as well as an overall, total allergy basis.

In addition, it is respectfully pointed out that the Phase II cat data presented in Applicants' disclosure is statistically significant as stated, for example, at page 23, lines 19-25, as follows.

> Analysis of the primary efficacy data for the study revealed a significant dose response relationship which was considered statistically significant (Figure 1) for control of allergic symptoms (nasal, lung, and total allergy) induced by cat room exposure at one and six weeks post treatment. Statistically significant, pair wise comparisons versus placebo for nasal and total allergy symptoms at 75 μg and 750μg was detected at six weeks (See Figure 1).

In sum, the test data from the human phase II study described in the specification is a statistically significant measurement of the efficacy of the claimed compositions in treating human cat allergies. The data is not a general "summary" but rather is presented as a quantified measurement of symptom improvements, both on a subgroup symptom basis and on a total, combined scale, following treatment with the claimed compositions. Data in this form is accepted in the art of immunotherapy and can be evaluated by any one ordinarily skilled in the art. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

In paragraph 18(C), the Examiner states that:

> the specification does not adequately describe the amino acid sequences of Amb a I peptide antigens, which portions of the Amb a I antigen would be nonimmunogenic, nor provide adequate guidance as to

which Amb a I peptides would reduce allergic responses to ragweed allergy in humans. Further, it would be unpredictable which dosages and routes of administration could be used with particular peptides. For instance, it would be unpredictable whether a particular peptide would induce tolerance by inducing suppresser T cells or affecting IgE responses when given orally or sublingually a peptidases and anatomic barriers in these sites would affect the biological half life and uptake of the peptide. Applicant may wish to consider incorporation of the essential portions of WO93/21321 which may describe particular Amb a I peptides into the instant specification.

The newly presented claims are directed to compositions containing at least one peptide having a reproducible, defined composition of amino acid residues and comprising at least one T cell epitope for a protein antigen. The claimed compositions are capable of down regulating an antigen specific immune response in a human sensitive to the protein antigen. At page 4, line 31, of the subject specification, Applicants teach that down regulation of an antigen specific immune response occurs when disease symptoms in a human sensitive to a protein antigen are reduced or eliminated, and/or the onset or progression of disease symptoms is prevented or slowed.

Applicants further teach methods for identifying peptides which comprise at least one T cell epitope of any protein antigen, including protein allergens (see e.g., page 9, beginning at line 16). These methods include testing overlapping peptides derived from an antigen in standard T cell proliferation assays, lymphokine secretion assays, and T cell non-responsiveness studies. Alternatively, an algorithm can be used for predicting those peptides which are likely to comprise T cell epitopes. These peptides can then be synthesized, purified, and tested for their ability to cause T cell proliferation, lymphokine secretion, or T cell non-responsiveness. In addition to such *in vitro* testing, peptides derived from protein antigens can also be tested in animal studies to evaluate the ability of T cell epitope containing peptides to down regulate the antigen specific immune response *in vivo*.

Applicants further teach at page 18, lines 1-6, that down regulation of an antigen specific immune response resulting from administration of T cell epitope-containing peptides derived from an antigen "may be determined clinically whenever possible depending on the disease condition being treated, or may be determined subjectively (i.e., the patient feels as if some or all of the symptoms related to the disease condition being treated have been alleviated." For clinical determination of antigen-specific immune response down regulation, Applicants teach several parameters which would be indicators of reduced responsiveness. For example, at page 6, beginning at line 31, Applicants teach that therapeutic compositions of the invention may cause T cell non-responsiveness to the offending antigen, measured by, for example, T cell proliferation assays. Alternatively, the compositions may modify the lymphokine secretion profile as compared with exposure to the naturally occurring offending antigen (e.g., result in a decrease of IL-4 and/or an increase in IL-2). The claimed compositions may also cause T cell subpopulations which normally participate in the response to the offending antigen to be drawn away from the sites of normal exposure (e.g., nasal mucosa, skin, lung) toward the sites of administration of the compound. Finally, Applicants teach that administration of the claimed compounds may also cause induction of T suppresser cells.

Based upon the above-summarized teachings provided in Applicants' disclosure, one of ordinary skill in the art using the techniques described by Applicants (e.g., assays which detect and/or measure T cell proliferation and lymphokine secretion, *in vivo* animal studies to assess down regulation, etc.) could select peptides from protein antigens, including protein allergens and autoantigen, which contain at least one T cell epitope, and then test these peptides either clinically or subjectively for their ability to down regulate an immune response against a particular antigen, as described above. Furthermore, the assays required to identify peptides which down regulate immune responses to antigen, would not require undue experimentation under 35 U.S.C. §112, first paragraph, since the

specification provides ample guidance with respect to the direction in which the experimentation should proceed. *In re Wands* 8 USPQ2d 1400, 1404 (CAFC 1988). Therefore, Applicants respectfully submit the peptides included in the compositions of the invention are enabled under section 112, first paragraph.

Furthermore, Applicant believes that it is not necessary to amend the specification to incorporate portions of any of the references cited in the specification and incorporated by reference, such as WO93/21321, as suggested by the Examiner in paragraph 18(C) of Paper No. 8 in view of the fact that they are pubic information. If the Examiner desires, Applicant to include some, Applicant will amend the specification pursuant to the Examiner's suggestion upon an indication of allowable subject matter.

In paragraph 20 of Paper No. 8, the Examiner rejects claims 1-43 under 35 U.S.C. §112, first paragraph, as the Examiner asserts that the disclosure is enabling only for claims limited to the particular antigens described in the specification (e.g., Peptide X and Peptide Y derived from the feline antigen, *Fel d* I). In particular, the Examiner states that:

> [o]ne with skill in the art would not have been enabled to make and use compositions or methods to treat allergic or autoimmune diseases without guidance as to which antigens are associated with particular autoimmune or allergic diseases. For instance, the specification does not disclose the autoantigens associated with the autoimmune diseases multiple sclerosis or diabetes. Secondly, in the absence of description by the disclosure, it would be unpredictable which portions of particular antigens would be nonimmunogenic, or what the amino acid sequences of such nonimmunogenic portions would be. Administration of immunogenic portions of an autoantigen or allergen would be expected to increase, rather than decrease the severity of allergic or autoimmune diseases. Therefore, one with skill in the art would not be enabled to make and use compositions to treat such diseases.

Applicants respectfully traverse this rejection. Applicants' disclosure provides a multiplicity of protein antigens, including protein allergens, known to cause certain

diseases which can be treated by the compositions and methods of the invention. For example with respect to protein allergens, at page 7, line 27, Applicants teach protein allergens from a variety of species including mite, cat, dog, grasses (e.g., rye, Johnson, Bermuda, etc.), ragweed, and Japanese cedar pollen. Applicants also teach numerous autoantigens known to those skilled in the art and the diseases with which they are associated (see, e.g., page 8, beginning at line 35, to page 9, line 15). These autoantigens include, for example, insulin; myelin basic protein; rh factor; acetylcholine receptors; thyroid cell receptors; basement membrane proteins; thyroid proteins; ICA-69 (PM-1); glutamic acid decarboxylase (64K or 65K); proteolipid protein (PLP), myelin associated glycoprotein (MAG), collagen (Type II), Heat Shock Protein and carboxypeptidase H). Applicants teach that these autoantigens are associated with such diseases as diabetes, rheumatoid arthritis, and multiple sclerosis. Applicants further teach several peptides having known T cell epitopes derived from autoantigens such as myelin oligodendrocyte protein (MOG), myelin basic protein (MBP), soluble Type II collagen, and insulin. Therefore, contrary to the Examiner assertion at page 5, lines 1-3, of Paper No. 8, the specification does disclose the autoantigens associated with various diseases including multiple sclerosis and diabetes.

Furthermore, in response to the Examiner's statement that "it would be unpredictable which portions of particular antigens would be nonimmunogenic," Applicants reiterate the arguments set forth above. In brief, the claimed compositions are administered to humans such that down regulation of an antigen specific immune response to an antigen of interest is achieved. One mode of achieving down regulation of an antigen specific immune response in a human is to administer the claimed composition in "non-immunogenic form". Peptides which contain at least one T cell epitope and thus are capable of eliciting a T cell response, such as stimulation, when administered in

immunogenic form are then capable of inducing T cell non-responsiveness or down regulation when administered in non-immunogenic fashion.

Rejection of Claims 1-43 Under 35 U.S.C. §103

In paragraph 22 of Paper No. 8, the Examiner rejects claims 1-43 under 35 U.S.C. §103 as being unpatentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991). In particular, the Examiner states that:

> Sehon et al. teach a variety of methods of making tolerogens from allergens and using such tolerogens to induce tolerance to particular allergens. Michael et al. teach how to make and use proteolytic fragments of pollen allergens to desensitize subjects to allergy. Litwin et al. teach how to make and use immunosuppressive peptide fragments of allergens to treat allergy. Kuo et al., see abstract and claims, teach modified Fel d I antigen and its use for inducing tolerance in cat allergic subjects.
>
> It would have been prima facie obvious to one of ordinary skill in the art to use the methods of the cited references to make modified, non-immunogenic allergen preparations for use in methods of desensitizing or inducing tolerance to particular allergens or autoantigens. Routine optimization of the dosage and mode of administration of the instant compositions fall within the ordinary skill of the art as evidenced by the cited references. Thus, claims 1-43 are prima facie obvious over the cited prior art.

Applicants respectfully traverse this rejection. It is respectfully submitted that none of the references cited by the Examiner, alone or in combination, teach or suggest the therapeutic compositions designed for human therapy or the methods for human therapy presently being claimed. For example, the combined teachings of the references do not teach or suggest a therapeutic composition containing a peptide having a ***reproducible, defined composition of amino acid residues and comprising at least one T cell epitope*** (each of the newly submitted independent claims with the exception of

claim 101). Furthermore, none of the teachings alone, or in combination teach or suggest a peptide purified to "at least about 90% purity" (independent claim 44) or a therapeutic composition containing a peptide having a particular "mean T cell stimulation index" (independent claim 49). In addition, the combined teachings fail to teach or suggest a therapeutic composition containing a peptide having "at least about 20% of the T cell epitopes of a protein antigen" (independent claim 56), or a therapeutic composition containing a peptide present in a particular dosage range (independent claim 62). The combined teachings of the cited references are even further removed from teaching or suggesting the methods of treating humans using such compositions.

Sehon et al. teach the conversion of a variety of allergens into tolerogenic compounds by conjugation with nonimmunogenic polymers such as isologous immunoglobulins, polyvinyl alcohols, and monomethoxy polyethylene glycols. Sehon et al. fail to teach or suggest the use of an isolated, unconjugated peptide to down regulate an antigen specific immune response. Therefore, Sehon et al. would not have provided any motivation whatsoever for one ordinarily skilled in the art at the time of Applicants' invention to have tried using a highly purified peptide containing at least one T cell epitope and administered in non-immunogenic form to down regulate an antigen specific immune response, as claimed by Applicants. The Examiner agreed during the personal interview that Sehon et al. does not teach or suggest the use of a peptide *per se* or a therapeutic composition containing a peptide.

Michael et al. teach a pollen allergen desensitizing product which is obtained from proteolytic digestion of a primary pollen allergen to produce a pollen specific polypeptide fraction having a molecular weight of about 10,000 Da and which is free from peptides which react with antibody to the allergen (and consequently does not contain any antigen). The pollen specific polypeptide fraction is preferably coadministered with adjuvants to achieve greater efficacy in desensitization by blocking the immune response.

In contrast, the therapeutic compositions claimed by Applicants are comprised of peptides which contain at least one T cell epitope for a protein antigen and have a ***reproducible, defined composition of amino acid residues***. In contrast, Michael et al. teach the use of a protein fraction from an enzymatic digest of a pollen allergen having a mixture of polypeptide components, each having an unknown composition of amino acid residues. Further, the process by which Michael et al. produces the protein fraction (i.e., proteolytic digestion) results in a product (i.e., a mixture of polypeptide components) which is ***not*** reproducible. Therefore, Michael et al. teach directly away from Applicants' invention which provides compositions including at least one peptide having a ***reproducible, defined composition of amino acid residues and comprising at least one T cell epitope***. Accordingly, at the time of Applicants' invention, one ordinarily skilled in the art would not have been motivated to have prepared therapeutic compositions as presently claimed.

Litwin et al. teach the use of peptic fragment fractions of a short ragweed fraction, enriched for *Amb a* I, to treat humans with ragweed hayfever. To obtain the peptic fragment fractions, ragweed pollen extracts are enzymatically digested and samples which are enriched for *Amb a* I, but contain other protein contaminants, are then obtained by chromatographic fractionation. Thus, the peptic fragment fractions taught by Litwin et al. are ***impure*** mixtures of ragweed proteins which do not have a ***reproducible, defined composition of amino acid residues*** as required for use in the claimed therapeutic compositions.

In contrast, as stated above with regard to regard to Michael et al. the therapeutic compositions claimed by Applicants require the presence of at least one peptide having a ***reproducible, defined composition of amino acid residues and comprising a T cell epitope***. In contrast, similar to Michael et al., Litwin et al. teach the use of peptide fragments (i.e., impure mixtures of ragweed pollen proteins and polypeptides), from an

enzymatic digest of ragweed pollen extracts, each fragment having an unknown composition of amino acid residues. Further, as with Michael et al., the method by which Litwin et al. produces the peptide fragments (i.e., enzymatic digestion) results in a product (i.e., a mixture of polypeptide components) which is ***not*** reproducible. Therefore, Litwin et al. teach directly away from Applicants' invention which provides compositions including at least one peptide having a ***reproducible, defined composition of amino acid residues and comprising at least one T cell epitope***.

Kuo teaches modified *Fel d* I protein which is capable of stimulating T cells from a cat allergic individual and which interacts with human IgE from a cat allergic individual to a lesser extent than does unmodified, affinity purified *Fel d* I. The *Fel d* I protein taught by Kuo is modified by treatment with mild base or alkali conditions, resulting in removal of some or all of the IgE reactive portions of the protein.

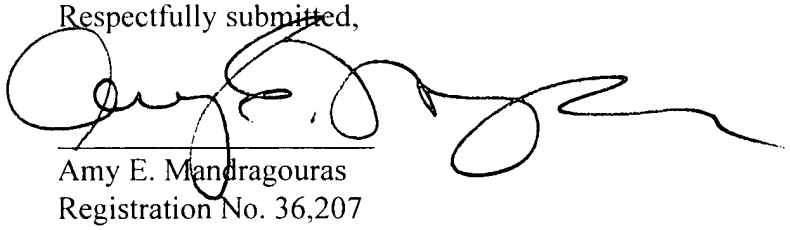
In contrast to the modified *Fel d* I protein taught by Kuo, Applicants are claiming peptides or compositions containing peptides useful for human administration. The Examiner agreed during the personal interview that Kuo et al. does not teach or suggest peptides or compositions containing peptides useful for human administration.

CONCLUSION

In view of the foregoing arguments, reconsideration of the rejections and allowance of new claims 44-102 is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at the number listed below.

Respectfully submitted,



Amy E. Mandragouras
Registration No. 36,207
Attorney for Applicants

LAHIVE & COCKFIELD
60 State Street
Boston, MA 02109
Tel. (617) 227-7400

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